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(54) PROCESS FOR THE PREPARATION OF ANHYDROUS AND HYDRATED ACTIVE PHARMACEUTICAL INGREDIENTS (APIS); STABLE PHARMACEUTICAL COMPOSITIONS PREPARED FROM THE SAME AND USES OF SAID COMPOSITIONS

VERFAHREN ZUR HERSTELLUNG VON WASSERFREIEN UND HYDRATISIERTEN PHARMAZEUTISCHEN WIRKSTOFFEN (APIS); AUS DIESEN HERGESTELLTE STABILE PHARMAZEUTISCHE ZUSAMMENSETZUNGEN UND ANWENDUNGEN FÜR DIESE ZUSAMMENSETZUNGEN

PROCEDE DE PREPARATION D'INGREDIENTS PHARMACEUTIQUES ACTIFS HYDRATES ET ANHYDRES (API), COMPOSITIONS PHARMACEUTIQUES STABLES PREPAREES A PARTIR DE CES DERNIERS ET UTILISATIONS DESDITES COMPOSITIONS

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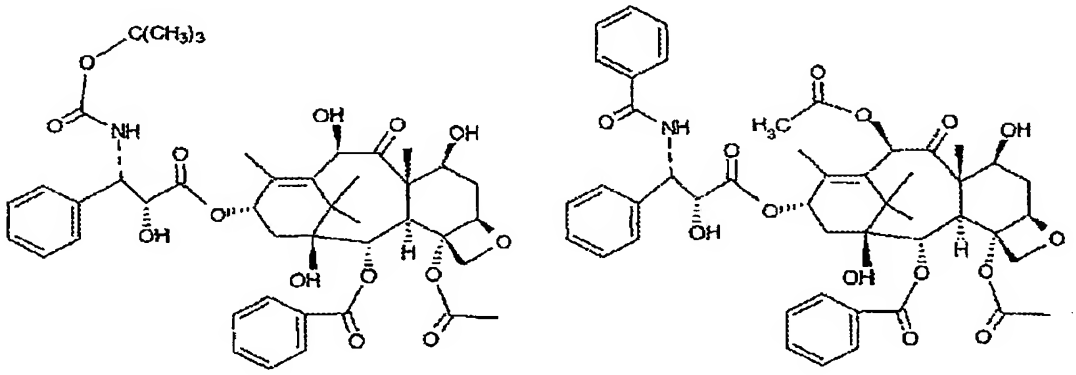
Description

Scope of the invention

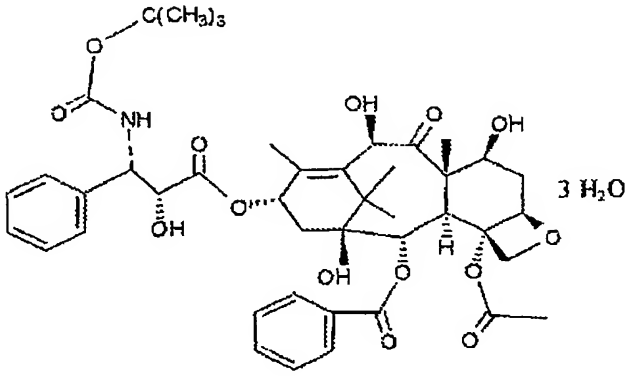
[0001] The present invention relates to a process for the preparation of API's, more specifically, taxane derivatives, especially (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-p-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I) and 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hidroxy-9-oxo-tax-11-en-13α-yl (2R, 3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II).



I

II

[0002] One innovative aspect of the present invention refers to a process particularly useful for obtaining anhydrous compounds which form hydrates thermolabile, which prevents the removal of water by conventional processes such as drying under vacuum at elevated temperatures. more specifically taxane derivatives especially the tri-hydrate of (2R, 3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (III).



III

[0003] Yet another innovative aspect of the present invention is with respect to a process for the preparation of injectable solutions, which are sterile and stable, from the API's according to the processes herein described, which are useful in the treatment of disease or infirmity, including, but not limited to, neoplastic tumors and other conditions which respond to treatment with agents that inhibit the depolymerization of tubulin, for example, cancers of the breast, ovaries, lungs and others.

[0004] The solutions are obtained by way of dissolution of the active principle I, II or III indicated above, in an appropriate biocompatible vehicle, followed by filtration through a membrane having a porosity less than or equal to 0.45 μm; or,

dissolution of the active principle I, II or III in an appropriate biocompatible vehicle, previously acidified with an organic or inorganic acid, followed by filtration through a membrane having a porosity less than or equal to 0.45 μm; or, dissolution of the active principle I, II or III in an appropriate biocompatible vehicle, posteriorly acidified, with an organic or inorganic acid followed by filtration through a membrane having a porosity less than or equal to 0.45 μm.

[0005] Lastly, the invention is also with respect to the stable pharmaceutical compositions thus obtained and the use of these compositions in the treatment of disease or infirmity, including, but not limited to, neoplastic tumors and other conditions which respond to treatment with agents that inhibit the depolymerization of tubulin, for example, cancers of the breast, ovaries, lungs and others.

Prior art

[0006] The active principle (2R, 3S) 4-acetoxy-2-α-benxoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I), a taxane derivative obtained by chemical semi-synthesis, which presents anti-cancer and anti-leukemic properties.

[0007] US patent 5,504,102 issued to Bristol-Myers Squibb describes a process for the preparation of polyethoxylated castor oil with low alkalinity and the use of this medium for the preparation of solutions containing antineoplastic agents.

[0008] Additionally, US patent 5, 698,582 issued to Rhone-Poulenc Rorer S.A. describes a process for the preparation of compositions containing taxane derivatives in a surfactant and the utility of these compositions for preparing perfusions.

[0009] Nonetheless, neither of these patents describe, nor do they suggest specifically, the use of anhydrous active principles in conjunction with polyethoxylated sorbitols which have been previously or posteriorly acidified for the preparation of sterile, injectable solutions, which confers additional stability two the compositions.

[0010] Brazilian patent application PI 9508789-3A, whose priority is French patent FR 94 08479 issued to Rhone-Poulenc Rorer S.A., describes a process for the preparation of the tri-hydrate of (2R, 3S) 4-acetoxy-2-α-bensoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (III), employing recrystallization from "a mixture of water and an aliphatic alcohol containg between 1 and 3 carbons, followed by drying the product obtained under pro-determined conditions of temperature, pressure and humidity."

[0011] The patent in question also maintains that the tri-hydrate (III) obtained "presents clearly superior stability relative to the anhydrous product".

[0012] However, comparative studies realized in our laboratories have demonstrates that, when stored under adequate and controlled conditions, the anhydrous product (I) obtained by the processes claimed herein demonstrates a stability equal or superior to the tri-hydrate and, that under these condition of storage, the product does not rehydrate to a significant degree.

[0013] It has been observed that utilisation of the anhydrous product (I), cited above, confers an equal or superior stability to the pharmaceutical finished dosage form, which can be illustrated by stability studies of solutions of anhydrous (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I) in polyethoxylated sorbitol which has been previously or posteriorly acidified.

[0014] Brazilian patent application PI 9508789-3 cites as an example the addition of ascorbic acid in the preparation of the tri-hydrate of (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, via recrystallization, which involves a laborious and multi-step process, to confer additional stability to the API.

[0015] Therefore, patent application PI 9508789-3, cited here as a reference, neither describes nor anticipates in a manner obvious to a person skilled in the art, the process for the preparation of the anhydrous product (I), as claimed in the present invention, which may be obtained directly and with fewer experimental steps.

[0016] Furthermore, patent application PI 9508789-3 does not anticipate nor suggest in a manner obvious to a person skilled in the art, the additional stability conferred to pharmaceutical formulations by addition of an organic or inorganic acid as claimed in the present invention.

[0017] On the other hand, US patent 5,698,582 describes a process for the preparation of solutions containing taxane derivatives in surfactants and the utilization of the same to prepare perfusions. This process requires that the active principle be first dissolved in ethanol, folowed by addition of a surfactant and subsequent removal of the ethanol under vacuum.

[0018] This process involves several steps and manipulations which makes it complex, laborious and lengthy. The process claimed in the present invention overcomes these disadvantages.

Detailed description of the invention

[0019] In a first embodiment, the present invention is advantageous with respect to the state of the art in that it is not necessary to recrystallize the active principle (III), with the concommitant reduction in the overall yield of the process. The anhydrous active principle (I) may be obtained directly, in a single production step, resulting in considerable economy

and a reduction in the number of steps.

[0020] In a second embodiment, the present invention also permits that, by use of the process described, (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I), of high purity, may be obtained in the form of an amorphous powder, which greatly facilitates its solubilization in biocompatible excipients. This results in the formation of solutions appropriate to be used directly in the confection of injectable pharmaceutical finished dosage forms without the addition of ethanol or other complementary excipients.

[0021] In a third embodiment, while the state of the art mentions that the addition of ascorbic acid during the recrystallization of the active principle (III) confers additional stability to it, an innovation particular to the present invention lies in the fact that it is advantageous to add a weak acid during the preparation of pharmaceutical solutions of (I) and (III). This is niether mentioned nor suggested by the state of the art.

[0022] As such, additional stability may be conferred to the finished dosage forms by addition of a weak acid to the solution. Acids which may be employed include, but are not limited to: ascorbic, phosphoric, acetic, citric or tartaric acid.

[0023] A fourth embodiment of the present invention lies in the fact that it is not necessary to first solubilize the active principle in ethanol followed by the subsequent removal of the ethanol as described in US patent 5,698,582.

[0024] As proposed herein, the compounds (I) and (II) may bye solubilized directly in the vehicle utilized in the formulation without the necessity of adding a co-solvent.

[0025] In a fifth embodiment of the present invention, it is possible to obtain stable, sterile pharmaceutical presentations, absent of pyrogens, of small, medium and large volume, which are appropriate for administration after dilution, or for filling in ampuoles, vials or other suitable recipients.

[0026] In a sixth embodiment, the present invention also describes a process for the preparation of concentrated solutions of 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hidroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate, (II) in polyethoxylated sorbitols.

[0027] The state of the art utilise as a vehicle for the formulation of (II) a mixture of polyethoxylated castor oil, for example, Cremophor® EL or ELP and ethanol. It is well known that Cremophor® is responsible for various adverse reactions which requires premedication with antihistamines, corticosteroids and/or H_2 antagonists).

[0028] Known commercial formulations also utilize considerable amounts of ethanol, which is responsible on many occasions for ethanol intoxication of the patient due to the large volume of product administered to achieve the desired therapeutic effect.

[0029] As such, the exclusion of polyethoxylated castor oil and ethanol from the compositions of the present invention presents considerable advantages from the patient point of view, and greatly reduce or eliminate the side-effects associated with these vehicles.

[0030] The process for the preparation of anhydrous API's according to the present invention, more specifically taxane derivatives, and especially (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I) and 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hidroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II) may be realized according to various procedures as will become evident.

[0031] In a seventh embodiment of the present invention, an hydrated sample of (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (I) is solubilized in a chemically inert solvent which forms an azeotrope with water. This solvent may be a linear or branched alcohol, an organic acid, a halogenated solvent, an aromatic solvent or another solvent of sufficient polarity capable of solubilizing the hydrated product. Preferably the solvent employed in the present invention is a short chain linear or branched alcohol.

[0032] The solution thus obtained is subjected to azeotropic distillation at a temperature between -20 and 200°C, and at a pressure between 1 and 800 mm Hg to remove the water of hydration. In the case of hydrated (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1, 7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, the temperature is, preferably, below 40°C.

[0033] In an eighth embodiment of the present invention, the hydrated (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate may also be solubilized in a combination of two or more of the aforementioned solvents.

[0034] For example, these solvents may be a combination of a linear or branched alcohol, an organic acid, a halogenated solvent, an aromatic solvent or another solvent of sufficient polarity capable of solubilizing the hydrated product and capable of forming a binary, ternary or quarternary azeotrope with water.

[0035] In the case of hydrated (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, the proportion between the first and second solvent is on the order of between 1:2 to 1:90.

[0036] Afterwards, the azeotropic distillation may be carried out at a pressure between <0.001 and 780 mmHg. In the case of hydrated (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-3-oxo-tax-11-en-13α-yl 3-tert-

butoxycaybonylamino-2-hydroxy-3-phenylpropionate, the pressure is preferentially between 0.1-100 mm Hg.

[0037] In a ninth embodiment of the present invention, there is also described the preparation of sterile, stable solutions of anhydrous or tri-hydrated, (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, (I) or (III), and also, 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hidroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II), in a biocompatible vehicle.

[0038] Appropriate vehicles include, but are not limited to, polyethoxylated sorbitols, and, preferentially polysorbate 80. The solutions are prepared by the slow addition of anhydrous or tri-hydrated (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, (I) or (III), or, 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hidroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II) to the vehicle with agitation, preferably, in an inert atmosphere, at a concentration between 1 and 100 mg of active ingredient on an anhydrous basis per mL polysorbate 80.

[0039] As an illustrative point, schematic figures of the present invention are presented in which:

Figure 1-refers to a schematic representation of the filtration process, as constituted in "Scheme 1";

Figure 2-refers to a schematic representation of the dissolution and filtration process as constituted in "Scheme 2".

[0040] With respect to the elements depicted in Figure 1, number (1) represents a sterilizing membrane employed in the filtration with a porosity of 0.22 μm. The pressurized vessel is represented by number (2) and the receipient for the sterilized filtrate is represented by number (3). N_2 represents the pressure inlet for an inert gas such as nitrogen. The combination of these elements constitues "Scheme 1".

[0041] With respect to Figure 2, the following elements are depicted: reactor (4), temperature control (5), control for agitation (6), sterilizing filtration membrane (7), and the receipient for the sterilized filtrate (8). N_2 represents the pressure inlet for an inert gas such as nitrogen. The combination of these elements constitues "Scheme 2".

[0042] According to scheme 1, figure 1, after complete solubilization of the active principle, the solution is transferred to a pressure vessel (2), filtered through the sterilizing membrane with a porosity of less than 0.95 μm, preferably 0.22 μm and filled into pyrogen free, sterile recipient(s) (3) in a sterile environment. The products thus obtained are stable for at least 18 months when stored between 2-8°C.

[0043] The preparation of sterile, stable solutions of anhydrous or tri-hydrated (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, (I) or (III), and also, 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hidroxy-9-oxo-tax-11-en-13α-yl (2R, 3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II), in a biocompatible vehicle, may also be conducted in an alternative manner.

[0044] Appropriate vehicles include, but are not limited to, polyethoxylated sorbitols, and, preferably, polysorbate 80.

[0045] The solution is prepared directly in a stainless steel reactor (4), as shown in figure 2, by way of slow addition of the active principle (I), (II) or (III) to the vehicle with internal agitation, preferably under an inert atmosphere, at a concentration between 1 and 100 mg of active principle (on an anhydrous basis)/mL polysorbate 80.

[0046] According to scheme 2, after complete solubilisation of the active principle, the solution is filtered directly through the sterilizing membrane (7) with a porosity of less than 0.45 μm, preferably 0.22 μm and collected in a sterile recipient (8) in a sterile environment. The solution thus obtained may be filled into pyrogen free, sterile vials, ampuoles or other suitable recipient. The products thus obtained are stable for at least 18 months when stored between 2-8°C.

[0047] In a tenth embodiment of the present invention, the aforementioned vehicles may be previously or posteriorly acidified. It is advantageous to acidify the polysorbate 80 prior to the audition of the active principle with an organic, inorganic or mixture of acids, chemically compatible with the vehicle and active principle (I, II or III), including, but not limited to, phosphoric, acetic, citric, tartaric or ascorbic acids.

[0048] It is also advantageous to acidify the solution of the active principle in polysorbate 80 after the complete dissolution of the active principle (I), (II) or (III) with an organic, inorganic or mixture of acids, chemically compatible with the vehicle and active principle (I, II or III), including, but not limited to, phosphoric, acetic, citric, tartaric or ascorbic, acids.

[0049] The solutions thus obtained are more stable than solutions which are not acidified. For the purpose of the present invention, the preferable acids to be employed are acetic or ascorbic. The pH may be adjusted between 3.0 -. 6.5, preferably, between 3.5 and 4.5. Solutions prepared in this manner are stable for at least 24 months when stored between 2 and 3°C (Tables 1 and 2).

TABLE 1:

Comparative stability study of solutions of the tri-hydrate and anhydrous forms of (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate in polysorbate 80 with and without the addition of acid

Time (months)	A% Docetaxel (trihydrate)	A% Docetaxel (anhydrous)	A% Docetaxel (anhydrous) with acetic acid	A% Docetaxel (anhydrous) with ascorbic acid
0	100,10	99,87	100,04	99,98
3	100,07	99,72	99,89	99,72
6	99,23	99,02	99,03	99,34
12	97,41	97,21	98,98	98,79
18	96,23	96,09	98,13	98,02
24	94,14	90,09	97,67	97,48

Note 1: All solutions were prepared at a concentration of 40 mg/mL, on an anhydrous basis, followed by filtration through a sterilizing mambrane.
Note 2: The acidified solutions were prepared from polysorbate 80 whose pH had been previously adjusted to between 3.5 and 4.5 by addition of the respective acids.
Note 3: Samples were stored between 2 and 8°C.
Note 4: Assay of docetaxel was performed by HPLC.

TABLE 2:

Comparative stability study of 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hidroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzolamino-2-hydroxy-3-phenylpropionate (II) in Cremophor EL and polysorbate 80 with and without addition of ascorbic acid

Time (months)	A% Paclitaxel (Cremophor EL)	A% Paclitaxel Anhydrous (polysorbate 80)	A% Paclitaxel Anhydrous (polysorbate 80 W/ascorbic acid)
0	100,08	100,55	100,30
3	99,46	100,10	100,20
6	99,04	99,81	99,99
12	96,46	97,02	97,90
18	92,10	93,05	97,01
24	85,16	89,84	94,97

Note 1: All solutions were prepared at a concentration of 6 mg/mL on an anhydrous basis, followed by filtration through a sterilizing membrane.
Note 2: The acidified solutions were prepared from polysorbate 80 whose pH had been previously adjusted to between 3.5 and 4.5 by addition of the respective acids.
Note 3: Samples were stored between 2 and 8°C
Note 4: Assay of paclitaxel was performed by HPLC

[0050] In a eleventh and final embodiment of the present invention, the solutions obtained by the processes heretofore described are useful in the treatment of disease or infirmity, including, but not limited to, neoplastic tumors and other conditions which respond to treatment with agents that inhibit the depolymerization of tubulin, for example, cancers of the breast, ovaries, lungs and others.

EXAMPLE 1:

Process for the removal of water of hydration by way of azeotropic distillation under vacuum

[0051] A 1.00 g [1.16 mMol] sample of hydrated (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (6.27 % water) was solubilized in 50 mL of reagent grade ethanol. The solution which was obtained was distilled under vacuum to remove the ethanol. The amorphous powder obtained was dried between 30 and 60 °C to constant weight, yielding 0.93g of anhydrous (2R, 3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate containing 0.10% water by KF titration.

EXAMPLE 2:

Process for the removal of water of hydration by way of binary azeotropic distillation under vacuum

[0052] A 1.00 g [1.16 mMol] sample of hydrated (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate (6.27 % water) was solubilized in 20 mL of ethanol. This was followed by the addition of 180 mL of toluene. The solution thus obtained was distilled under vacuum (20 mm Hg/40 °C) to remove, firstly the ethanol. The azeotrope formed between toluene and water was then distilled at 1 mm Hg/28 °C. Finally, the remainder of the toluene was removed and the amorphous powder obtained was dried at a temperature around 50 °C until constant weight, yielding 0.92 g of anhydrous (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate ester containing 0.12% water by KF titration.

EXAMPLE 3 :

Process for the preparation of a stable and sterile solution of anhydrous (2R,35) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hyfroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate ester in polysorbate 80 (with compressed air agitation)

[0053] In a beaker equipped with a helical compressed air agitator, under an atmosphere of N_2 was added 100 mL of polysorbate 80. This was followed by the slow addition of 4.00g of anhydrous (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-apoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate. Agitation was maintained until complete solubilization of the active ingredient. The resulting solution was transferred to a pressurized vessel and filtered through a 0.22 μm sterilizing membrane, in a sterile environment under pressure and then filled in vials using customary procedures. The solution thus obtained was shown to be stable for 18 months when stored at temperatures between 2 and 8 °C.

EXAMPLE 4 :

Process for the preparation of a stable and sterile, solution of anhydrous (2R,3S) 4-acetoxy-2-α-benzoyloxyx-5β-20-epoxy 1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-text-butoxycarbonylamino-2-hydroxy-3-phenylpropionate in polysorbate 80 (using a stainless steel reactor)

[0054] In a stainless steel reactor equipped with an internal agitation system, under an atmosphere of N_2 was added 100 mL of polysorbate 80. This was followed by the slow addition of 4.00g of anhydrous (2R, 3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate. Agitation was maintained until complete solubilization of the active ingredient. The resulting solution was filtered through a 0.22 μm sterilizing membrane coupled to the reactor, in a sterile environment under pressure, and then filled in vials using customary procedures. The solution thus obtained was shown to be stable for 18 months when stored at temperatures between 2 and 8 °C.

EXAMPLE 5 :

Process for the preparation of a stable and sterile solution of anhydrous (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-tax-11-en-3α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate in previously acidified polysorbate 80 (with compressed air agitation)

[0055] In a beaker equipped with a helical compressed air agitator, under an atmosphere of N_2 was added 100 mL of polysorbate 80 which had been previous acidified with ascorbic acid to a pH of 3.9. This was followed by the slow addition of 4.00g of anhydrous (2R,33) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate. Agitation was maintained until complete solubilization of the active ingredient. The resulting solution was transferred to a pressurized vessel and filtered through a 0.22 μm sterilizing membrane, in a sterile environment under pressure, and then filled in vials using customary procedures. The solution thus obtained was shown to be stable for 24 months when stored at temperatures between 2 and 8°C.

EXAMPLE 6:

Process for the preparation of a stable and sterile solution of anhydrous (2R, 3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy 1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-an-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate in previously acidified polysorbate 80 (using a stainless steel reactor)

[0056] In a stainless steel reactor equipped with an internal agitation system, under an atmosphere of N_2 was added 100 mL of polysorbate 80 which had been previous acidified with ascorbic acid to a pH of 3.9. This was followed by the slow addition of 4.00g of anhydrous (2R, 3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate. Agitation was maintained until complete solubilization of the active ingredient. The resulting solution was filtered through a 0.22 μm sterilizing membrane coupled to the reactor, in a sterile environment under pressure , and then filled in vials using customary procedures. The solution thus obtained was shown to be stable for 24 months when stored at temperatures between 2 and 8 °C .

EXAMPLE 7:

Process for the preparation of a stable and sterile solution of anhydrous (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate in posteriorly acidified polysorbate 80 (with compressed air Agitation)

[0057] In a beaker equipped with a helical compressed air agitator, under an atmosphere of N_2 was added 100 mL of polysorbate 80. This was followed by the slow addition of 4.00g of anhydrous (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate. Agitation was maintained until complete solubilization of the active ingredient. The resulting solution was then acidified with ascorbic acid to a pH of 4.0. The resulting solution was transferred to a pressurized vessel and filtered through a 0.22 μm sterilizing membrane, in a sterile environment under pressure, and then filled in vials using customary procedures. The solution thus obtained was shown to be stable for 24 months when stored at temperatures between 2 and 8°C.

EXAMPLE 8:

Process for the preparation of a stable and solutions of the tri-hydrate of (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydro-3-phenylpropionate in previously acidified polysorbate 80 (with compressed air agitation)

[0058] In a beaker equipped with a helical compressed air agitator, under an atmosphere of N_2 was added 100 mL of polysorbate 80 which had been previous acidified with ascorbic acid to a pH of 4.0. This was followed by the slow addition of 4.27 g of the tri-hydrate of (2R, 3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate. Agitation was maintained until complete solubilization of the active ingredient. The resulting solution was transferred to a pressurized vessel and filtered through a 0.22 μm sterilizing membrane, in a sterile environment under pressure, and then filled in vials using customary procedures. The solution thus obtained was shown to be stable for 24 months when stored at temperatures between 2 and 8°C .

EXAMPLE 9:

Process for the preparation of a stable and sterile solutions of the tri-hydrate of (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate in previously acidified polysorbate 80 (using a stainless steel reactor)

[0059] In a stainless steel reactor equipped with an internal agitation system, under an atmosphere, of N_2 was added 100 mL of polysorbate 80 which had been previous acidified with ascorbic acid to a pH of 3.9. This was followed by the slow addition of 4.27g of the tri-hydrate of (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate. Agitation was maintained until complete solubilization of the active ingredient. The resulting solution was filtered through a 0.22 μm sterilizing membrane coupled to the reactor, in a sterile environment under pressure, and then filled in vials using customary procedures. The solution thus obtained was shown to be stable for 24 months when stored at temperatures between 2 and 8 °C.

EXAMPLE 10:

Process for the preparation of a stable and sterile solution of the tri-hydrate of (2R,3S) 4-acetoxy-2-α-benzoyloxy- 5β- 20-epoxy- 1,7-β- 10-β- tri- hydroxy- 9-oxo- tax- 11-en- 13α-yl 3-tert- butoxycarbonylamino- 2-hydroxy-3-phenylpropionate in posteriorly acidified polysorbate 80 (with compressed air agitation)

[0060] In a beaker equipped with a helical compressed air agitator, under an atmosphere of N_2 was added 100 mL of polysorbate 80. This was followed by the slow addition of 4.27g of the tri-hydrate of (2R, 3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate. Agitation was maintained until complete solubilization of the active ingredient. The resulting solution was then acidified with ascorbic acid to a pH of 4.0 The resulting solution was transferred to a pressurized vessel and filtered through a 0.22 μm sterilizing membrane, in a sterile environment under pressure, and then filled in vials using customary procedures. The solution thus obtained was shown to be stable for 24 months when stored at temperatures between 2 and 8 °C.

EXAMPLE 11:

Process for the preparation of a stable and sterile solution of 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II) in polysorbate 80 (with compressed air agitation)

[0061] In a beaker equipped with a helical compressed air agitator, under an atmosphere of N_2 was added 100 mL of polysorbate 80. This was followed by the slow addition of 0.6g anhydrous 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R, 3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II). Agitation was maintained until complete solubilization of the active ingredient. The resulting solution was transferred to a pressurized vessel and filtered through a 0.22 μm sterilizing membrane, in a sterile environment under pressure, and then filled in vials using customary procedures. The solutions thus obtained was shown to be stable for 18 months when stored at temperatures between 2 and 8 °C.

EXAMPLE 12:

Process for the preparation of a stable and sterile solution of 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II) in polysorbate 80 (using a stainless steel reactor)

[0062] In a stainless steel reactor equipped with an internal agitation system, order an atmosphere of N_2 was added 100 mL of polysorbate 80. This was followed by the slow addition of 0.6 g of anhydrous 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate. Agitation was maintained until complete solubilization of the active ingredient. The resulting solution was filtered through a 0.22 μm sterilizing membrane coupled to the reactor, in a sterile environment under pressure, and then filled in was using customary procedures. The solution thus obtained was shown to be stable for 18 months when stored at temperatures between 2 and 8 °C.

EXAMPLE 13:

Process for the preparation of a stable and sterile solution of 4-acetoxy-2-oxo-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II) in previously acidified polysorbate 80 (with compressed air agitation)

[0063] In a beaker equipped with a helical compressed air agitator, under an atmosphere of H_2 was added 100 of polysorbate 80 which had been previous acidified with ascorbic acid to a pH between 3.5 and 4.5. This was followed by the slow addition of 0.60 g of 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R, 3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate. Agitation was maintained until complete solubilization of the active ingredient. The resulting solution was transferred to a pressurised vessel and filtered through a 0.22 μm sterilizing membrane, in a sterile environment under pressure, and then filled in vials using customary procedures. The solution thus obtained was shown to be stable for 24 months when stored at temperatures between 2 and 8°C.

EXAMPLE 14:

Process for the preparation of a stable and sterile solution of 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II) in previously acidified polysorbate 80 (using a stainless steel reactor)

[0064] In a stainless steel reactor equipped with an internal agitation system, under an atmosphere of N_2 was added 100 mL of polysorbate 80 which had been previous acidified with ascorbic acid to a pH between 3.5 and 4.5. This was followed by the slow addition of 0.60 g of 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpronionate. Agitation was maintained until complete solubilization of the active ingredient. The resulting solution was filtered through a 0.22 μm sterilizing membrane coupled to the reactor, in a sterile environment under pressure, and then filled in vials using customary procedures. The solution thus obtained was shown to be stable for 24 months when stored at temperatures between 2 and 8°C.

EXAMPLE 15:

Process for the prepartion of a stable and sterile solution of 4-acetoxy-2-α-benzoyloxy-5-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate (II) in posteriorly acidified polysorbate 80 (with compressed air agitation)

[0065] In a beaker equipped with a helical compressed air agitator, under an atmosphere of N_2 was added 100 mL of polysorbate 80. This was followed by the slow addition of 0.60 g of 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate. Agitation was maintained until complete solubilization of the active ingredient. The resulting solution was acidified with ascorbic acid to a pH between 3.5 and 4.5 and then transferred to a pressurized vessel and filtered through a 0.22 μm sterilizing membrane, in a sterile environment under pressure, and then filled in vials using customary procedures. The solution thus obtained was shown to be stable for 24 months when stored at temperatures between 2 and 8°C.

Comparative stability study between the tri-hydrate and anhydrous forms of (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate

[0066]

Time (months)	A% Docetaxel (trihydrate)[1]	A% Impurities (unknown)	Assay H_2O[2]	A% Docetaxel (anhydrous)[3]	A% Impurities (unknown)	Assay H_2O
0	99,51	0,49	6,32	99,28	0,72	0,10
3	99,23	0,77	6,35	99,21	0,79	0,11
6	99,30	0,70	6,21	99,26	0,73	0,12
12	98,91	1,09	6,42	98,93	1,07	0,09

(continued)

Time (months)	A% Docetaxel (trihydrate)[1]	A% Impurities (unknown)	Assay H_2O[2]	A% Docetaxel (anhydrous)[3]	A% Impurities (unknown)	Assay H_2O
18	98,72	1,28	6,31	98,65	1,35	0,12
24	98,21	1,79	6,29	98,29	1,71	0,13

Experimental data obtained in the laboratories of Quiral Quimica do Brasil S/A
[1] Prepared in the laboratories of Quiral Quimica do Brasil S/A.
[2] Water determined by Karl Fischer titration.
[3] Prepared according to EXAMPLE 2

[0067] Analysis was realized by HPLC using a Waters Spherisorb® C-18, 250 x 5 mm column, mobile phase MeOH: H_2O 85:15, flow 1.5 mL/min. Related impurities reported as A% discounting the peak due to the dead volume. Samples were stored in amber glass vials under N_2 in a dessicator over P_2O_5 maintained between ~5 and 0 °C.

[0068] The examples given in the present patent application are for illustrative purposes only and should not be construed as limiting the scope of the invention. Variations of the heretofore described processes which produce similar results will be apparent to persons skilled in the art.

Claims

1. A process, for the preparation of concentrated, sterile injectable solutions containing, as active pharmaceutical ingredient (API), a taxane derivative selected from the group consisting of docetaxel or paclitaxel, **characterized by** the following steps:

   A. Obtaining the anhydrous form of compounds (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, docetaxel (I) or 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R, 3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate, paclitaxel (II), in which the water content is lower than 1.0% w/w, by the substeps:

      (i) Solubilization of the respective hydrated forms in a solvent or in a chemically inert solvent mixture which forms an azeotrope with water and of sufficient polarity to effect complete solubilization of the active principles, chosen between polyethoxylated sorbitols, linear on bronched alcohols, organic acids, aliphatic or cyclic ethers, halogenated solvents, aromatic solvents, in a concentration range between 1 - 100 mg of the active principles to 1 mL of the solvent or solvent mixture;
      (ii) Removal of the water of hydration contained in the mixture (i) by azeotropic distillation at a temperature between -20 and 200 °C and at a pressure between <0.001 and 780 mm Hg, until the water content is lower than 1.0% w/w;

   B. Addition of an acid and/or a non-nucleophilic antioxidant to a biocompatible vehicle or excipient in,a sufficient quantity to adjust the pH in the range of 3.0 to 6.5;
   C. Addition of the amorphous solid, obtained by steps described in Ai-Aii, to the resulting solution of the step (B), slowly with agitation and in a temperature between 20 to 40 °C, until its complete solubilization and formation of a transparent solution, in which the concentration of the active principle in the vehicle or excipient is in the range from 1 to 100 mg/mL;
   D. Filtration of the concentrated solution obtained in (C) by passage through a sterilizing membrane having a porosity less than or equal to 0.45 μm.

2. A Process according to claim 1 **characterized by** the use of an anhydrous solvent or a mixture of solvents in steps Ai-Aii.

3. A process according to claim 1 **characterized in that** the anhydrous solvent employed in the steps Ai-Aii is an alcohol, an aliphatic or cyclic ether, an organic acid, a halogenated solvent or an aromatic solvent, destined to effect the solubilization of the hydrated taxane derivative.

4. A process according to claim 3 **Characterized in that** the solvent employed is a linear or branched chain biocompatible alcohol.

5. A process according to claim 4 **characterized in that** the alcohol employed is ethanol.

6. A process according to claim 1 **characterized in that** in step (A), the compound (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate docetaxel (I) or 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hidroxy-9-oxo-tax-11-en-13α-yl (2R, 3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate, paclitaxel (II), is hydrated with 1.1 to 20.0% w/w of water, the solvents employed in steps Ai-Aii are absolute ethanol and anhydrous toluene in a relative proportion of 1:9, at a temperature between 10 and 70°C and at a pressure between 10 and 100 mm Hg.

7. A process according to claim 6 **characterized in that** (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, docetaxel (I) or 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate, paclitaxel (II), is hydrated with 1.1 to 4.9% w/w of water.

8. A process according to claim 1 **characterized in that** the active ingredient obtained in step A is (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, docetaxel (I), in its anhydrous form, in which the water content is lower than 1.0% w/w.

9. A process according to claim 1 **characterized in that** the active principle employed as raw material in step Ai is (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate 3 H_2O or docetaxel trihydrate (III), in which the amount of hydration water is 5.0 to 6.8% w/w.

10. A process according to claim 1 **characterized in that** the active principle obtained in steps Ai-Aii is 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate, paclitaxel (II), in its anhydrous form, when the raw material employed in the step Ai corresponds to hydrated paclitaxel derivatives.

11. A process according to claim 1 **characterized by** slowly adding the active principle (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, anhydrous docetaxel (I) or 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate, anhydrous paclitaxel (II), obtained according to steps Ai-Aii, wherein the aim is its use according to the conditions described in steps (B) and (C), until its completely solubilization, with agitation and in an inert atmosphere, followed by filtration through a sterilizing membrane with porosity less or equal to 0.45 μm, as described in the step (D).

12. A process according to claim 1 **characterized by** slowly adding the active principle (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, docetaxel (I) or 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate, paclitaxel (II), in its anhydrous or hydrated forms, directly, to the resulting solution of step (B), following the others steps contained in the step (C) without the use of steps Ai-Aii, as well as the filtration step through a sterilizing membrane with porosity less or equal to 0.45 μm, as described in the step (D), with agitation and in an inert atmosphere.

13. A process according to the claims 1 to 12 **characterized in that** the final concentration obtained in the concentrated solution containing (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, docetaxel (I) or 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate, paclitaxel (II), is from 1 to 100 mg of the active principle, on an anhydrous basis, for each mL of the vehicle or excipient employed.

14. A process according to claim 1 **characterized in that** the vehicle employed is polysorbate 80 and the concentration range of (2R,3S) 4-acatoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, docetaxel (I), on an anhydrous basis, is from 20 to 60 mg/mL, and the sterilizing membrane employed in the filtration described in the step (D) have a porosity of 0.22 μm.

15. A process according to claim 1 **characterized in that** the vehicle employed is polysorbate 80 and the concentration range of 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate, paclitaxel (II), on an anhydrous basis, is from 10 to 100 mg/mL, and the sterilizing membrane employed in the filtration described in the step (D) have a porosity of 0.22 μm.

16. A process according to claim 1 **characterized by** using in step B polyethoxylated sorbitols as vehicles or excipients, previously acidified with non-nucleophilic acids until a pH range between 3.0 to 6.5, or during or after total solubilization of the active principle in the vehicle or excipient, foreseen in the stage C.

17. A process according to claim 16 **characterized in that** the polyethoxylated sorbitol employed is polysorbate 80.

18. A process according to claim 1 **characterized in that** the acid and/or non-nucleophilic antioxidant added to the active ingredient is pharmaceutically compatible and the vehicle or excipient used has antioxidant properties, and it is capable to adjust the pH of the pharmaceutical formulation in the range of 3.0 to 6.5.

19. A process according to claim 18 **characterized in that** the as a and/or non-nucleotide antioxidant employed is capable to adjust the pharmaceutical formulation pH in the range of 3.0 to 4.5.

20. A process according to claim 18, **characterized in that** the acid and/or non-nucleophilic antioxidant is an organic or inorganic acid, chosen among ascorbic, phosphoric, acetic, citric and tartaric acids.

21. A process according to claim 18 **characterized in that** a combination of one or more acids and/or non-nucleophilic antioxidants are employed.

22. A process according to claim 1 **characterized in that** the vehicle or excipient employed is polysorbate 80 and the acid and/or non-nucleophilic antioxidant is chosen from acetic, citric or ascorbic acids, or a combination thereof, added in a sufficient quantity to, at the end, the resultant injectable concentrated solution pH is in the range of 3.0 to 4.5.

23. A pharmaceutical composition, sterile, containing anhydrous taxane derivative, prepared according to the processes described in claims 1 to 22 **characterized by** consisting of (2R,3S) 4-acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl 3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, docetaxel (I), anhydrous, with water content lower (<) than 1.0% w/w, 40 mg; polysorbate 80, 1 mL; and acetic acid, or ascorbic acid or citric acid, in a sufficient quantity to obtain a pH in the range of 3.0 to 4.5 (respectively, 0.00445g - 0.00306g; 0.00445g - 0.00309g and 0.00307g - 0.00250g); and be filled in sterile and pirogenic free recipients, for single or multiple use.

24. A pharmaceutical composition, sterile, containing anhydrous taxane derivative, prepared according to the processes described in claims 1 to 22 **characterized by** consisting of 4-acetoxy-2-α-benzoyloxy-5-β-20-epoxy-1,7β-10-β-tri-hydroxy-9-oxo-tax-11-en-13α-yl (2R,3S) 3-benzoylamino-2-hydroxy-3-phenylpropionate, anhydrous Paclitaxel (II), with water content lower (<) than 1.0% w/w, 6.0 mg, calculated on an anhydrous basis; polysorbate 80, 1 mL; and acetic acid, or ascorbic acid or citric acid, in a sufficient quantity to obtain a pH in the range of 3.0 a 4.5 (respectively, 0.00445g - 0.00306g; 0.00445g - 0.00309g and 0.00307 - 0.00250); and be filled in sterile and pirogenic free recipients, for single for multiple use.

Patentansprüche

1. Verfahren zur Herstellung von konzentierten, sterilen Injektionslösungen, die als pharmazeutischen Wirkstoff (API, active pharmaceutical ingredient) ein Taxanderivat aus der Gruppe bestehend aus Docetaxel oder Paclitaxel enthalten, **dadurch gekennzeichnet, daß** man:

   A. die wasserfreie Form von Verbindungen (2R,3S)-4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-3-tert.-butoxycarbonylamino-2-hydroxy-3-phenyl-propionat, Docetaxel (I), oder 4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-(2R,3S)-3-benzoylamino-2-hydroxy-3-phenylpropionat, Paclitaxel (II), mit einem Wassergehalt von weniger als 1,0 Gew.-% durch die folgenden Unterschritte erhält:

      (i) Solubilisieren der jeweiligen hydratisierten Formen in einem Lösungsmittel oder in einem chemisch

inerten Lösungsmittelgemisch, das ein Azeotrop mit Wasser bildet und so polar ist, daß die Wirkstoffe vollständig solubilisiert werden, ausgewählt unter polyethoylierten Sorbitolen, linearen oder verzweigten Alkoholen, organischen Säuren, aliphatischen oder cyclischen Ethern, halogenierten Lösungsmitteln und aromatischen Lösungsmitteln, in einem Konzentrationsbereich zwischen 1-100 mg der Wirkstoffe auf 1 mL des Lösungsmittels oder Lösungsmittelgemischs;
(ii) Entfernen des in der Mischung (i) enthaltenen Hydratationswassers durch azeotrope Destillation bei einer Temperatur zwischen -20°C und 200°C und bei einem Druck zwischen <0,001 und 780 mm Hg, bis der Wassergehalt weniger als 1,0 Gew.-% beträgt;

B. eine Säure und/oder ein nichtnucleophiles Antioxidans in einer zur Einstellung des pH-Werts im Bereich von 3,0 bis 6,5 ausreichenden Menge zu einem biokompatiblen Vehikel oder Exzipienten gibt;
C. den durch die in Ai-Aii beschriebenen Schritte erhaltenen amorphen Feststoff langsam unter Rühren und bei einer Temperatur zwischen 20 bis 40°C zu der resultierenden Lösung aus Schritt (B) gibt, bis er vollständig solubilisiert ist und sich eine transparente Lösung bildet, wobei die Wirkstoffkonzentration in dem Vehikel oder Exzipienten im Bereich von 1 bis 100 mg/mL liegt;
D. die in (C) erhaltene konzentrierte Lösung über eine Sterilisationsmembran mit einer Porosität kleiner gleich 0,45 μm filtriert.

2. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** man in den Schritten Ai-Aii ein wasserfreies Lösungsmittel oder ein Lösungsmittelgemisch verwendet.

3. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** es sich bei dem in den Schritten Ai-Aii eingesetzten wasserfreien Lösungsmittel um einen Alkohol, einen aliphatischen oder cyclischen Ether, eine organische Säure, ein halogeniertes Lösungsmittel oder ein aromatisches Lösungsmittel, bestimmt zur Bewirkung der Solubilisierung des hydratisierten Taxanderivats, handelt.

4. Verfahren nach Anspruch 3, **dadurch gekennzeichnet, daß** es sich bei dem eingesetzten Lösungsmittel um einen linearen oder verzweigtkettigen biokompatiblen Alkohol handelt.

5. Verfahren nach Anspruch 4, **dadurch gekennzeichnet, daß** es sich bei dem eingesetzen Alkohol um Ethanol handelt.

6. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** in Schritt (A) die Verbindung (2R,3S)-4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-3-tert.-butoxycarbonylamino-2-hydroxy-3-phenylpropionat, Docetaxel (I), oder 4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-(2R,3S)-3-benzoylamino-2-hydroxy-3-phenyl-propionat, Paclitaxel (II), mit 1,1 bis 20,0 Gew.-% Wasser hydratisiert ist und es sich bei den in den Schritten Ai-Aii eingesetzten Lösungsmitteln um absolutes Ethanol und wasserfreies Toluol in einem relativen Verhältnis von 1:9 bei einer Temperatur zwischen 10 und 70°C und einem Druck zwischen 10 und 100 mm Hg handelt.

7. Verfahren nach Anspruch 6, **dadurch gekennzeichnet, daß** (2R,3S)-4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-3-tert.-butoxycarbonylamino-2-hydroxy-3-phenyl-propionat, Docetaxel (I), oder 4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-(2R,3S)-3-benzoylamino-2-hydroxy-3-phenylpropionat, Paclitaxel (II), mit 1,1 bis 4,9 Gew.-% Wasser hydratisiert ist.

8. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** es sich bei dem in Schritt A erhaltenen Wirkstoff um (2R,3S)-4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-3-tert.-butoxycarbonylamino-2-hydroxy-3-phenyl-propionat, Docetaxel (I), in seiner wasserfreien Form handelt, wobei der Wassergehalt weniger als 1,0 Gew.-% beträgt.

9. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** es sich bei dem in Schritt Ai als Ausgangsstoff eingesetzten Wirkstoff um (2R,3S)-4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-3-tert.-butoxycarbonylamino-2-hydroxy-3-phenylpropionat 3 H_2O bzw. Docetaxeltrihydrat (III) handelt, wobei die Hydratationswassermenge 5,0 bis 6,8 Gew.-% beträgt.

10. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** es sich bei dem in den Schritten Ai-Aii erhaltenen Wirkstoff um 4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-(2R,3S)-3-benzoylamino-2-hydroxy-3-phenyl-propionat, Paclitaxel (II), in seiner wasserfreien Form handelt, wenn der in Schritt Ai

eingesetzte Ausgangsstoff hydratisierten Paclitaxelderivaten entspricht.

11. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** man den gemäß den Schritten Ai-Aii erhaltenen Wirkstoff (2R,3S)-4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-3-tert.-butoxycarbonylamino-2-hydroxy-3-phenyl-propionat, wasserfreies Docetaxel (I), oder 4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxotax-11-en-13α-yl-(2R,3S)-3-benzoyl-amino-2-hydroxy-3-phenylpropionat, wasserfreies Paclitaxel (II), der gemäß den in den Schritten (B) und (C) beschriebenen Bedingungen verwendet werden soll, bis zu seiner vollständigen Solubilisierung unter Rühren und in einer Inertatmosphäre langsam zugibt und danach über eine Sterilisationsmembran mit einer Porosität kleiner gleich 0,45 μm filtriert, wie in Schritt (D) beschrieben.

12. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** man den Wirkstoff (2R,3S)-4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-3-tert.-butoxycarbonylamino-2-hydroxy-3-phenylpropionat, Docetaxel (I), oder 4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-tri-hydroxy-9-oxotax-11-en-13α-yl-(2R,3S)-3-benzoyl-amino-2-hydroxy-3-phenylpropionat, Paclitaxel (II), in seiner wasserfreien oder hydratisierten Form direkt ohne Verwendung der Schritte Ai-Aii unter Rühren und in einer Inertatmosphäre langsam zu der erhaltenen Lösung von Schritt (B) gibt und danach die anderen in Schritt (C) enthaltenen Schritte sowie den Schritt der Filtration über eine Sterilisationsmembran mit einer Porosität kleiner gleich 0,45 μm filtriert, wie in Schritt (D) beschrieben, durchführt.

13. Verfahren nach einem der Ansprüche 1 bis 12, **dadurch gekennzeichnet, daß** die in der (2R,3S)-4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-3-tert.-butoxycarbonylamino-2-hydroxy-3-phenylpropionat, Docetaxel (I), oder 4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-(2R,3S)-3-benzoylamino-2-hydroxy-3-phenyl-propionat, Paclitaxel (II), enthaltenden konzentrierten Lösung erhaltene Endkonzentration 1 bis 100 mg des Wirkstoffs auf wasserfreier Basis pro mL des eingesetzten Vehikels oder Exzipienten beträgt.

14. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** es sich bei dem eingesetzten Vehikel um Polysorbat 80 handelt und der Konzentrationsbereich von (2R,3S)-4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-3-tert.-butoxycarbonylamino-2-hydroxy-3-phenyl-propionat, Docetaxel (I), auf wasserfreier Basis 20 bis 60 mg/mL beträgt und die bei der in Schritt (D) beschriebenen Filtration eingesetzte Sterilisationsmembran eine Porosität von 0,22 μm aufweist.

15. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** es sich bei dem eingesetzten Vehikel um Polysorbat 80 handelt und der Konzentrationsbereich von 4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-(2R,3S)-3-benzoylamino-2-hydroxy-3-phenyl-propionat, Paclitaxel (II), auf wasserfreier Basis 10 bis 100 mg/mL beträgt und die bei der in Schritt (D) beschriebenen Filtration eingesetzte Sterilisationsmembran eine Porosität von 0,22 μm aufweist.

16. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** man in Schritt B oder während oder nach der in Stufe C vorgesehenen vollständigen Solubilisierung des Wirkstoffs in dem Vehikel oder Exzipienten vorher mit nichtnucleophilen Säuren bis zu einem pH-Bereich zwischen 3,0 und 6,5 angesäuerte polyethoxylierte Sorbitole als Vehikel oder Exzipienten verwendet.

17. Verfahren nach Anspruch 16, **dadurch gekennzeichnet, daß** es sich bei dem eingesetzten polyethoxylierten Sorbitol um Polysorbat 80 handelt.

18. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** die Säure und/oder das nichtnucleophile Antioxidans, die bzw. das dem Wirkstoff zugegeben wird, pharmazeutisch verträglich ist und das verwendete Vehikel oder der verwendete Exzipient antioxidative Eigenschaften aufweist und zur Einstellung des pH-Werts der pharmazeutischen Formulierung im Bereich von 3,0 bis 6,5 befähigt ist.

19. Verfahren nach Anspruch 18, **dadurch gekennzeichnet, daß** die eingesetzte Säure und/oder das eingesetzte nichtnucleophile Antioxidans zur Einstellung des pH-Werts der pharmazeutischen Formulierung im Bereich von 3,0 bis 4,5 befähigt ist.

20. Verfahren nach Anspruch 18, **dadurch gekennzeichnet, daß** es sich bei der Säure und/oder dem nichtnucleophilen Antioxidans um eine organische oder anorganische Säure, ausgewählt unter Ascorbinsäure, Phosphorsäure, Es-

sigsäure, Citronensäure und Weinsäure, handelt.

21. Verfahren nach Anspruch 18, **dadurch gekennzeichnet, daß** man eine Kombination von einer oder mehreren Säuren und/oder einem oder mehreren nichtnucleophilen Antioxidantien einsetzt.

22. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** es sich bei dem eingesetzten Vehikel oder Exzipienten um Polysorbat 80 handelt und die Säure und/oder das nichtnucleophile Antioxidans unter Essigsäure, Citronensäure oder Ascorbinsäure oder einer Kombination, zugegeben in einer so großen Menge, daß der pH-Wert der erhaltenen konzentrierten Injektionslösung am Ende im Bereich von 3,0 bis 4,5 liegt, ausgewählt wird.

23. Sterile pharmazeutische Zusammensetzung, enthaltend ein wasserfreies Taxanderivat, hergestellt nach den in den Ansprüchen 1 bis 22 beschriebenen Verfahren, **dadurch gekennzeichnet, daß** sie aus 40 mg wasserfreiem (2R, 3S)-4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-3-tert.-butoxycarbonyl-amino-2-hydroxy-3-phenylpropionat, Docetaxel (I), mit einem Wassergehalt von weniger (<) als 1,0 Gew.-%; 1 mL Polysorbat 80 und Essigsäure, Citronensäure oder Ascorbinsäure in einer so großen Menge, daß sich ein pH-Wert im Bereich von 3,0 bis 4,5 ergibt (respektive 0,00445 g - 0,00306 g; 0,00445 g - 0,00309 g und 0,00307 g bis 0,00250 g), besteht und in sterile und pyrogenfreie Behältnisse zur ein- oder mehrmaligen Verwendung abgefüllt ist.

24. Sterile pharmazeutische Zusammensetzung, enthaltend ein wasserfreies Taxanderivat, hergestellt nach den in den Ansprüchen 1 bis 22 beschriebenen Verfahren, **dadurch gekennzeichnet, daß** sie aus 6,0 mg wasserfreiem 4-Acetoxy-2-α-benzoyloxy-5β-20-epoxy-1,7-β-10-β-trihydroxy-9-oxotax-11-en-13α-yl-(2R,3S)-3-benzoylamino-2-hydroxy-3-phenyl-propionat, Paclitaxel (II), mit einem Wassergehalt von weniger (<) als 1,0 Gew.-%, auf wasserfreier Basis berechnet; 1 mL Polysorbat 80 und Essigsäure, Citronensäure oder Ascorbinsäure in einer so großen Menge, daß sich ein pH-Wert im Bereich von 3,0 bis 4,5 ergibt (respektive 0,00445 g - 0,00306 g; 0,00445 g - 0,00309 g und 0,00307 g bis 0,00250 g), besteht und in sterile und pyrogenfreie Behältnisse zur ein- oder mehrmaligen Verwendung abgefüllt ist.

Revendications

1. Procédé de préparation de solutions injectables concentrées stériles contenant, à titre de principe actif pharmaceutique (PAP), un dérivé du taxane choisi dans le groupe constitué de docétaxel ou de paclitaxel, **caractérisé par** les étapes suivantes :

   A. l'obtention de la forme anhydre des composés 3-tert-butoxycarbonylamino-2-hydroxy-3-phénylpropionate de (2R,3S)-4-acétoxy-2-α-benzoyloxy-5β-20-époxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-én-13α-yle, docétaxel (I) ou (2R,3S)-3-benzoylamino-2-hydroxy-3-phénylpropionate de 4-acétoxy-2-σ-benzoyloxy-5-β-20-époxy-1,7β-10-β-trihydroxy-9-oxo-tax-11-én-13α-yle, paclitaxel (II), dans laquelle la teneur en eau est inférieure à 1, 0 % p/p, par les étapes sous-suivantes :

      (i) la solubilisation des formes hydratées respectives dans un solvant ou dans un mélange de solvants chimiquement inertes qui forme un azéotrope avec l'eau et de polarité suffisante pour assurer la solubilisation totale des principes actifs, choisi parmi les sorbitols polyéthoxylés, les alcools linéaires ou ramifiés, les acides organiques, les éthers aliphatiques ou cycliques, les solvants halogénés, les solvants aromatiques, dans une gamme de concentration comprise entre 1 et 100 mg des principes actifs pour 1 ml du solvant ou du mélange de solvants ;
      (ii) l'élimination de l'eau d'hydratation contenue dans le mélange (i) par distillation azéotrope à une température comprise entre -20 et 200 °C et à une pression comprise entre < 0,001 et 780 mmHg, jusqu'à ce que la teneur en eau soit inférieure à 1,0 % p/p ;

   B. l'addition d'un acide et/ou d'un antioxydant non nucléophile à un véhicule ou excipient biocompatible dans une quantité suffisante pour ajuster le pH dans la gamme de 3,0 à 6, 5 ;
   C. l'addition du solide amorphe, obtenu par les étapes décrites dans Ai-Aii, à la solution résultante de l'étape (B), lentement sous agitation et à une température comprise entre 20 et 40 °C, jusqu'à sa solubilisation totale et la formation d'une solution transparente, dans laquelle la concentration du principe actif dans le véhicule ou l'excipient est dans la gamme de 1 à 100 mg/ml ;
   D. la filtration de la solution concentrée obtenue en (C) par passage sur une membrane stérilisante ayant une porosité inférieure ou égale à 0,45 μm.

2. Procédé selon la revendication 1, **caractérisé par** l'utilisation d'un solvant anhydre ou d'un mélange de solvants dans les étapes Ai-Aii.

3. Procédé selon la revendication 1, **caractérisé en ce que** le solvant anhydre utilisé dans les étapes Ai-Aii est un alcool, un éther aliphatique ou cyclique, un acide organique, un solvant halogéné ou un solvant aromatique, destiné à assurer la solubilisation du dérivé de taxane hydraté.

4. Procédé selon la revendication 3, **caractérisé en ce que** le solvant utilisé est un alcool biocompatible à chaîne linéaire ou ramifiée.

5. Procédé selon la revendication 4, **caractérisé en ce que** l'alcool utilisé est l'éthanol.

6. Procédé selon la revendication 1, **caractérisé en ce que** dans l'étape (A), le composé 3-tert-butoxycarbonylamino-2-hydroxy-3-phénylpropionate de (2R,3S)-4-acétoxy-2-α-benzoyloxy-5β-20-époxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-én-13α-yle, docétaxel (I) ou (2R,3S)-3-benzoylamino-2-hydroxy-3-phénylpropionate de 4-acétoxy-2-α-benzoyloxy-5-β-20-époxy-1,7β-10-β-trihydroxy-9-oxo-tax-11-én-13α-yle, paclitaxel (II), est hydraté avec 1,1 à 20,0 % p/p d'eau, les solvants utilisés dans les étapes Ai-Aii sont l'éthanol absolu et le toluène anhydre dans une proportion relative de 1:9, à une température comprise entre 10 et 70°C et à une pression comprise entre 10 et 100 mmHg.

7. Procédé selon la revendication 6, **caractérisé en ce que** le 3-tert-butoxycarbonylamino-2-hydroxy-3-phénylpropionate de (2R,3S)-4-acétoxy-2-α-benzoyloxy-5β-20-époxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-én-13α-yle, docétaxel (I) ou le (2R,3S)-3-benzoylamino-2-hydroxy-3-phénylpropionate de 4-acétoxy-2-α-benzoyloxy-5-β-20-époxy-1,7β-10-β-trihydroxy-9-oxo-tax-11-én-13α-yle, paclitaxel (II), est hydraté avec 1,1 à 4,9 % p/p d'eau.

8. Procédé selon la revendication 1, **caractérisé en ce que** le principe actif obtenu dans l'étape A est le 3-tert-butoxycarbonylamino-2-hydroxy-3-phénylpropionate de (2R,3S)-4-acétoxy-2-α-benzoyloxy-5β-20-époxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-én-13α-yle, docétaxel (I), sous sa forme anhydre, dans laquelle la teneur en eau est inférieure à 1,0 % p/p.

9. Procédé selon la revendication 1, **caractérisé en ce que** le principe actif utilisé comme matière première dans l'étape Ai est le 3-tert-butoxycarbonylamino-2-hydroxy-3-phénylpropionate de (2R,35)-4-acétoxy-2-α-benzoyloxy-5β-20-époxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-én-13α-yle 3 H_2O ou docétaxel trihydraté (III), dans lequel la quantité d'eau d'hydratation est de 5,0 à 6,8 % p/p.

10. Procédé selon la revendication 1, **caractérisé en ce que** le principe actif obtenu dans les étapes Ai-Aii est le (2R, 3S)-3-benzoylamino-2-hydroxy-3-phénylpropionate de 4-acétoxy-2-α-benzoyloxy-5-β-20-époxy-1,7β-10-β-trihydroxy-9-oxo-tax-11-én-13α-yle, paclitaxel (II), sous sa forme anhydre, lorsque la matière première utilisée dans l'étape Ai correspond à des dérivés de paclitaxel hydratés.

11. Procédé selon la revendication 1, **caractérisé par** l'addition lente du principe actif 3-tert-butoxycarbonylamino-2-hydroxy-3-phénylpropionate de (2R,3S) -4-acétoxy-2-α-benzoyloxy-5β-20-époxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-én-13α-yle, docétaxel anhydre (I) ou (2R,3S)-3-benzoylamino-2-hydroxy-3-phénylpropionate de 4-acétoxy-2-α-benzoyloxy-5-β-20-époxy-1,7β-10-β-trihydroxy-9-oxo-tax-11-én-13α-yle, paclitaxel anhydre (II), obtenu selon les étapes Ai-Aii, le but étant son utilisation selon les conditions décrites dans les étapes (B) et (C), jusqu'à sa solubilisation totale, sous agitation et sous une atmosphère inerte, suivie de filtration sur une membrane stérilisante ayant une porosité inférieure ou égale à 0,45 μm, comme décrit dans l'étape (D).

12. Procédé selon la revendication 1, **caractérisé par** l'addition lente du principe actif 3-tert-butoxycarbonylamino-2-hydroxy-3-phénylpropionate de (2R,3S)-4-acétoxy-2-α-benzoyloxy-5β-20-époxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-én-13α-yle, docétaxel (I) ou (2R,3S)-3-benzoylamino-2-hydroxy-3-phénylpropionate de 4-acétoxy-2-α-benzoyloxy-5-β-20-époxy-1,7β-10-β-trihydroxy-9-oxo-tax-11-én-13α-yle, paclitaxel (II), sous ses formes anhydre ou hydratée, directement, à la solution résultante de l'étape (B), suivant les autres étapes de l'étape (C), sans l'utilisation des étapes Ai-Aii, ainsi que l'étape de filtration sur une membrane stérilisante ayant une porosité inférieure ou égale à 0,45 μm, comme décrit dans l'étape (D), sous agitation et dans une atmosphère inerte.

13. Procédé selon les revendications 1 à 12, **caractérisé en ce que** la concentration finale obtenue dans la solution concentrée contenant le 3-tert-butoxycarbonylamino-2-hydroxy-3-phénylpropionate de (2R,3S)-4-acétoxy-2-α-benzoyloxy-5β-20-époxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-én-13α-yle, docétaxel (I) ou le (2R,3S)-3-benzoylamino-

2-hydroxy-3-phénylpropionate de 4-acétoxy-2-α-benzoyloxy-5-β-20-époxy-1,7β-10-β-trihydroxy-9-oxo-tax-11-én-13α-yle, paclitaxel (II), est de 1 à 100 mg du principe actif, sur une base anhydre, pour chaque ml de véhicule ou d'excipient utilisé.

14. Procédé selon la revendication 1, **caractérisé en ce que** le véhicule utilisé est le polysorbate 80 et la gamme de concentration de 3-tert-butoxycarbonylamino-2-hydroxy-3-phénylpropionate de (2R,3S)-4-acétoxy-2-α-benzoyloxy-5β-20-époxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-én-13α-yle, docétaxel (I), sur une base anhydre, est de 20 à 60 mg/ml, et la membrane stérilisante utilisée dans la filtration décrite dans l'étape (D) a une porosité de 0,22 μm.

15. Procédé selon la revendication 1, **caractérisé en ce que** le véhicule utilisé est le polysorbate 80 et la gamme de concentration de (2R,3S)-3-benzoylamino-2-hydroxy-3-phénylpropionate de 4-acétoxy-2-α-benzoyloxy-5-β-20-époxy-1,7β-10-β-trihydroxy-9-oxo-tax-11-én-13α-yle, paclitaxel (II), sur une base anhydre, est de 10 à 100 mg/ml, et la membrane stérilisante utilisée dans la filtration décrite dans l'étape (D) a une porosité de 0,22 μm.

16. Procédé selon la revendication 1, **caractérisé par** l'utilisation dans l'étape B de sorbitols polyéthoxylés comme véhicules ou excipients, acidifiés préalablement avec des acides non nucléophiles jusqu'à une gamme de pH comprise entre 3,0 et 6,5, ou pendant ou après la solubilisation totale du principe actif dans le véhicule ou l'excipient, prévue dans l'étape C.

17. Procédé selon la revendication 16, **caractérisé en ce que** le sorbitol polyéthoxylé utilisé est le polysorbate 80.

18. Procédé selon la revendication 1, **caractérisé en ce que** l'acide et/ou l'antioxydant non nucléophile ajouté au principe actif est pharmaceutiquement compatible et le véhicule ou excipient utilisé a des propriétés antioxydantes et il est capable d'ajuster le pH de la formulation pharmaceutique dans la gamme de 3,0 à 6,5.

19. Procédé selon la revendication 18, **caractérisé en ce que** l'acide et/ou l'antioxydant non nucléophile utilisé est capable d'ajuster le pH de la formulation pharmaceutique dans la gamme de 3,0 à 4,5.

20. Procédé selon la revendication 18, **caractérisé en ce que** l'acide et/ou l'antioxydant non nucléophile est un acide organique ou minéral, choisi parmi les acides ascorbique, phosphorique, acétique, citrique et tartrique.

21. Procédé selon la revendication 18, **caractérisé en ce qu'**on utilise une combinaison d'un ou plusieurs acides et/ou antioxydants non nucléophiles.

22. Procédé selon la revendication 1, **caractérisé en ce que** le véhicule ou excipient utilisé est le polysorbate 80 et l'acide et/ou l'antioxydant non nucléophile est choisi parmi les acides acétique, citrique et ascorbique, ou une combinaison de ceux-ci, ajoutés en quantité suffisante de sorte que, à la fin, le pH de la solution concentrée injectable résultante soit dans la gamme de 3,0 à 4,5.

23. Composition pharmaceutique, stérile, contenant du dérivé du taxane anhydre, préparée selon les procédés décrits dans les revendications 1 à 22, **caractérisée en ce qu'**elle est constituée de 3-tert-butoxycarbonylamino-2-hydroxy-3-phénylpropionate de (2R,3S)-4-acétoxy-2-α-benzoyloxy-5β-20-époxy-1,7-β-10-β-tri-hydroxy-9-oxo-tax-11-én-13α-yle, docétaxel (I), anhydre, la teneur en eau étant inférieure à (<) 1,0 % p/p, 40 mg ; de polysorbate 80, 1 ml ; et d'acide acétique, ou d'acide ascorbique ou d'acide citrique, en quantité suffisante pour obtenir un pH dans la gamme de 3,0 à 4,5 (respectivement, 0,00445 g - 0,00306 g ; 0,00445 g - 0,00309 g et 0,00307 g - 0,00250 g) ; et on remplit des récipients stériles et apyrogènes, pour une utilisation unique ou multiple.

24. Composition pharmaceutique, stérile, contenant du dérivé du taxane anhydre, préparée selon les procédés décrits dans les revendications 1 à 22, **caractérisée en ce qu'**elle est constituée de (2R,3S)-3-benzoylamino-2-hydroxy-3-phénylpropionate de 4-acétoxy-2-α-benzoyloxy-5-β-20-époxy-1,7β-10-β-trihydroxy-9-oxo-tax-11-én-13α-yle, paclitaxel anhydre (II), la teneur en eau étant inférieure à (<) 1,0 % p/p, 6,0 mg, calculée sur une base anhydre ; de polysorbate 80, 1 ml ; et d'acide acétique, ou d'acide ascorbique ou d'acide citrique, en quantité suffisante pour obtenir un pH dans la gamme de 3,0 à 4,5 (respectivement, 0,00445 g - 0,00306 g ; 0,00445 g - 0,00309 g et 0,00307 g - 0,00250 g) ; et on remplit des récipients stériles et apyrogènes, pour une utilisation unique ou multiple.

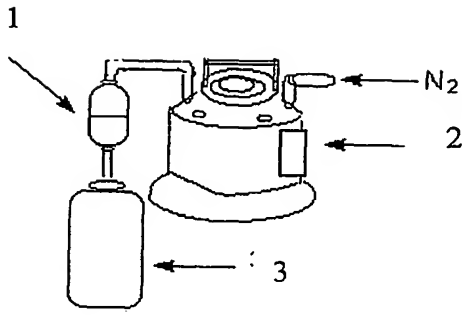


FIGURE 1

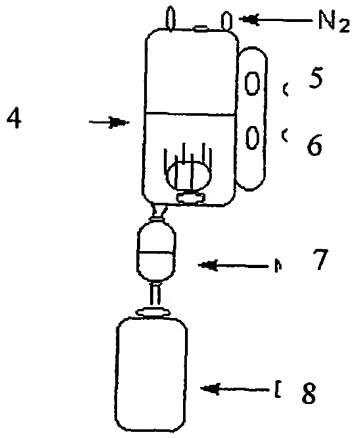


FIGURE 2

REFERENCES CITED IN THE DESCRIPTION

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